Glucocorticoids, Oral Summary

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FDA-APPROVED INDICATIONS AND DOSAGES[1,2,3,4,5,6,7,8,9,10,11,12,13,14]

Drug	Manufacturer	Dosage	Availability
betamethasone (Celestone Soluspan®)	Merck	Adults and adolescents: 0.6 to 7.2 mg per day depending on specific condition treated Children: 0.02 to 0.3 mg/kg/day in 3 or 4 divided doses, depending on the specific condition treated	Oral solution: 0.6 mg/5 mL
budesonide (Entocort® EC)	generic, Perrigo	*Treatment of mild to moderate active Crohn's disease*: Adults: 9 mg once daily in the morning for up to 8 weeks. Repeated 8 week courses can be given for recurring episodes of active disease Children 8 to 17 years who weigh more than 25 kg: 9 mg orally once daily for up to 8 weeks, followed by 6 mg once daily for 2 weeks *Maintenance of clinical remission of mild to moderate Crohn's disease*: Adults: 6 mg once daily for up to 3 months. Treatment for > 3 months has not been shown to be beneficial	Enteric-coated capsule: 3 mg
budesonide extended-release (Uceris®)	Santarus	*Induction of remission in adults with active, mild to moderate ulcerative colitis:* 9 mg orally once daily in the morning with or without food for up to 8 weeks	Extended-release capsule: 9 mg
cortisone	generic	25-300 mg per day or on alternate days, depending on specific condition treated	Tablet: 25 mg
deflazacort (Emflaza™)	Marathon	*Treatment of Duchenne muscular dystrophy (DMD):* Patients 5 years of age and older: 0.9 mg/kg/day; discontinue gradually when administered for more than a few days Tablets may be crushed and mixed with applesauce; the dose should be consumed immediately The oral suspension should be mixed with 3 to 4 ounces of juice (except grapefruit juice) or milk and administered immediately Unused drug should be discarded 1 month after opening the container	Tablet: 6 mg, 18 mg, 30 mg, 36 mg Oral suspension: 22.75 mg/mL

FDA Approved Indications and Dosages (continued)

Drug	Manufacturer	Dosage	Availability
dexamethasone (Dexpak®, Dexamethasone Intensol, Locort 7-Day, Locort 11-Day, Zodex 6-Day, Zodex 12-Day, ZonaCort 7-Day, ZonaCort 11-Day)	generic, Valeant, Roxane, Allegis Holding, Xspire, Key Therapeutics	Adults: 0.75 to 9 mg per day, in 2 to 4 divided doses, depending on specific condition treated Children: 0.03-0.3 mg/kg per day, in 2 to 4 divided doses, depending on the specific condition treated; For Locort 7-Day, Locort 11-Day, ZonaCort 7 and ZonaCort 11 *only* – 0.02 to 0.3 mcg/kg/day in 3 to 4 divided doses	Tablet: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg; Dexpak: 1.5 mg tablets in 6, 10, and 13 day supply (taperpak); Elixir: 0.5 mg/ml; Oral solution: 0.5 mg/5 mL; Intensol oral solution: 1 mg/mL; Locort and ZonaCort: 1.5 mg tablets; 27 tablets in 7 day supply and 41 tablets in 11 day supply blister packs Zodex: 1.5 mg tablets; 21 tablets in 6 day supply and 49 tablets in 12 day supply packs
hydrocortisone (Cortef®)	generic, Pfizer	Adults: 20-240 mg per day, in 2 to 4 divided doses, depending on specific condition treated Children: 2-8 mg/kg per day, in 3 to 4 divided doses, depending on specific condition treated	Tablet: 5 mg, 10 mg, 20 mg
methylprednisolone (Medrol®)	generic, Pfizer	Adults: *General dosage*: 4-48 mg per day in 4 divided doses *Hypercalcemia associated with certain types of cancer*: 32-80 mg per day *Tuberculous meningitis*: 48-64 mg per day; gradually taper after 1 to 2 weeks and stop by 4 to 6 weeks Children: 0.5-1.7 mg/kg per day in 2 to 4 divided doses, depending on specific condition treated	Tablet: 2, 4, 8, 16, 32; 4 mg in 21-tablet dosepak
prednisolone (Flo-Pred®, Millipred®, Orapred®, Orapred ODT®, Pediapred®, Prelone®)	generic, Concordia, Taro, Zylera, Mission, Seton, Shionogi, Teva	Adults: 5-60 mg per day in 3 to 4 divided doses, depending on specific condition treated Children: 0.14-2 mg/kg per day in 3 to 4 divided doses	Tablet: 5 mg; 5 mg in 6 day 21-tablet and 12 day 48-tablet dose packs Oral liquid: 5 mg/5 mL, 10 mg/5mL, 15 mg/5 mL, 20 mg/5 mL, and 25 mg/5 mL Orally disintegrating tablet: 10, 15, and 30 mg

FDA Approved Indications and Dosages (continued)

Drug	Manufacturer	Dosage	Availability
prednisone	generic	*Primary or secondary adrenocortical insufficiency*: Adults: 5 mg each morning, 2.5 mg each evening Children: 4-5 mg/m2 given 1 to 4 times per day *Congenital adrenal hyperplasia:* Adults: 2.5-5 mg once daily at bedtime Children: 12-13 mg/m2 given in 2 to 3 divided doses *Other indications to modify the body's immune response:* Adults: 5-100 mg daily, depending on specific diagnosis and patient response Children: 0.05-2 mg/kg per day, depending on specific diagnosis and patient response	Tablet: 1, 2.5, 5, 10, 20, and 50 mg Oral solution: 5 mg/5 mL
prednisone delayed-release (Rayos®)	Horizon	Adults and Children: *Initial dose*: 5 mg administered once daily *Maintenance dose*: Use lowest dosage that will maintain an adequate clinical response, depending on specific condition treated Swallow tablet whole	Tablet: 1, 2, and 5 mg
prednisone (Prednisone Intensol)	Roxane	Adults and Children: 5-60 mg per day, depending on specific condition treated	Oral solution: 5 mg/mL (contains 30% alcohol)

OVERVIEW[15,16,17,18,19,20]

Corticosteroids are naturally occurring hormones, produced by the adrenal glands. They are classified in 2 categories, glucocorticoids and mineralocorticoids, based on their primary pharmacological activity. Mineralocorticoids alter fluid and electrolyte balance by facilitating sodium resorption and hydrogen and potassium excretion in the kidneys. Glucocorticoids influence a number of metabolic pathways including protein metabolism, lipolysis, gluconeogenesis, and glycogenesis. Glucocorticoids also exert some mineralocorticoid effects. The oral corticosteroids discussed in this review are considered glucocorticoids; however, cortisone and hydrocortisone possess both glucocorticoid and mineralocorticoid properties.

Glucocorticoids mediate a variety of inflammatory and immune responses including: the decrease of the formation and release of endogenous inflammatory mediators (e.g., prostaglandins, kinins, histamine, and the complement system); inhibition of macrophage and leukocyte activity in inflamed areas; blockage of the release of allergic response mediators (e.g., histamine, leukotrienes, cytokines, and prostaglandins); and inhibition of IgE synthesis.

Due to their anti-inflammatory or immunosuppressive effects, these agents are used for allergic, dermatologic, gastrointestinal, hematologic, ophthalmologic, nervous system (multiple sclerosis exacerbation), renal, respiratory, and neoplastic and rheumatologic conditions, as well as for specific infectious diseases and organ transplantation. Additional uses include the treatment of certain endocrine conditions and palliation of certain neoplastic diseases. Budesonide (Entocort EC) is indicated only for treatment and maintenance of remission of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. Emflaza (deflazacort) is indicated only for the

treatment of Duchenne muscular dystrophy (DMD), a genetic disorder characterized by progressive muscle degeneration and weakness. It primarily affects males, occurring in approximately 1 in 3,600 male births. According to the National Adrenal Diseases Foundation, hydrocortisone or cortisone are the glucocorticoid agents of choice for Addison's disease or secondary adrenocortical insufficiency.[21] The Endocrine Society recommendations for treatment of primary adrenal insufficiency (Addison's disease) include glucocorticoids (hydrocortisone or cortisone acetate) and fludrocortisone in adults and hydrocortisone in children.[22]

PHARMACOKINETICS[23,24,25,26]

Cortisone is rapidly metabolized to hydrocortisone (Cortef) following absorption; therefore, cortisone and hydrocortisone are considered therapeutically equivalent. Both agents have a short period of biologic activity (8 to 12 hours).

Methylprednisolone (Medrol), prednisolone (Millipred, Orapred), and prednisone (Prednisone Intensol, Rayos) possess intermediate-acting biologic activity (18 to 36 hours). Prednisone is rapidly metabolized to prednisolone; these agents are generally considered to be interchangeable. Prednisone delayed-release tablets (Rayos) consist of a prednisone-containing core tablet in an inactive shell, which delays the onset of *in vitro* drug dissolution by approximately 4 hours. Patients currently on immediate-release prednisone, prednisolone, or methylprednisolone can be switched to prednisone delayed-release tablets at an equivalent dose based on relative potency.

Betamethasone (Celestone) and dexamethasone (Dexpak, Dexamethasone Intensol, Locort, Zodex, ZonaCort) have relatively long-acting biological activity (35 to 54 hours).

Budesonide enteric-coated (Entocort EC) contains granules that are coated to protect dissolution in gastric juice, which dissolve at a pH >5.5 in the duodenum. Thereafter, a matrix of ethylcellulose with budesonide controls the release of drug in the intestinal lumen in a time-dependent manner. The intrinsic potency of budesonide is about 15-fold that of prednisolone.

Deflazacort is a corticosteroid prodrug. It is an oxazoline derivative of prednisolone. Its active metabolite, 21-desDFZ, provides anti-inflammatory and immunosuppressive effects. The exact mechanism for its therapeutic effects on DMD is unknown; *in vivo,* deflazacort has been found to promote myofiber repair, proliferation, and function.

For the purpose of comparison, the following is the equivalent milligram dosage of certain glucocorticoids:

Drug	Dose (mg)
betamethasone	0.75
dexamethasone	0.75
methylprednisolone	4
prednisolone	5
prednisone	5
deflazacort	6
hydrocortisone	20
cortisone	25

SPECIAL USAGE CONSIDERATIONS[27,28,29,30,31,32,33]

Agents in this review are contraindicated in patients with a history of hypersensitivity to any component of the product. Cortisone, hydrocortisone, prednisolone, and prednisone are also contraindicated in those with systemic fungal infections.

Glucocorticoids can alter endocrine function leading to reversible hypothalamic-pituitary adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia. Patients should be monitored for these conditions with chronic use.

While used for the short-term treatment of acute exacerbations of chronic inflammatory bowel disease, such as ulcerative colitis and Crohn's disease, glucocorticoids should not be used in patients who are at increased risk of gastrointestinal perforation, such as those with diverticulitis. In addition, glucocorticoids should not be used in patients with peptic ulcer disease except under life-threatening circumstances.

Patients may experience elevated blood pressure, hypokalemia, and salt and water retention. Blood pressure and sodium and potassium levels should be monitored with chronic use. Glucocorticoids should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Glucocorticoid use has been associated with mental status effects, such as euphoria, insomnia, mood swings, personality changes, severe depression, and psychotic manifestations. These reactions may improve after either dose reduction or withdrawal, although pharmacologic treatment may be necessary.

Ophthalmic effects of glucocorticoid therapy include cataracts, glaucoma, and optic neuritis. Intraocular pressure should be monitored if therapy is prescribed for more than 6 weeks. Corticosteroids are not recommended for patients with active ocular herpes simplex.

Acute myopathy has occurred with the use of high doses of glucocorticoids, usually in patients with disorders of neuromuscular disorders, such as myasthenia gravis. Clinical improvement or recovery may take weeks to years after discontinuation of glucocorticoid therapy.

Decreased bone formation, increased bone resorption, and inhibition of osteoblast function are effects of glucocorticoid therapy and can lead to osteoporosis at any age. Bone density should be monitored in patients on long-term therapy.

Patients may have increased susceptibility to infection, including new infections or reactivation of latent infections.

Administration of live or live-attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Response to killed or inactivated vaccines cannot be predicted.

Children treated with glucocorticoids may experience a decrease in growth velocity. Linear growth should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits of corticosteroid therapy and the availability of other treatment alternatives. Children should be titrated to the lowest effective dose and prolonged therapy should be avoided in order to minimize potential growth effects. Safety and efficacy of budesonide (Entocort EC) and cortisone has not been established in pediatric patients. Safety and efficacy of deflazacort (Emflaza) tablets and oral suspension have not been established in patients less than 5 years of age. In addition,

deflazacort oral suspension contains benzyl alcohol, which can lead to serious and life-threatening reactions, such as gasping syndrome, in neonates and low birth weight infants.

Use of glucocorticoids during the first trimester of pregnancy can cause fetal harm, such as orofacial clefts, intrauterine growth restriction, and decreased birth weight. Risks and benefits of therapy should be considered. Most agents in this review are rated Pregnancy Category C; however, cortisone and some specific prednisolone and prednisone products (Flo-Pred, Rayos) are Pregnancy Category D.

Dosage adjustments of glucocorticoids are not required for patients with renal impairment. However, patients with hepatic disease can have an exaggerated response to systemic corticosteroids. In general, a dose reduction should be considered for patients with moderate to severe liver disease. Monitor for signs and symptoms of hypercorticism. Prednisolone is preferred to prednisone in patients with significant hepatic disease because prednisolone does not require hepatic activation. Product labeling advises that no dosage adjustment is needed with deflazacort in patients with mild or moderate hepatic impairment; clinical experience is lacking with severe impairment.

Common adverse reactions for glucocorticoids include fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.

Concurrent use of glucocorticoids with various medications may lead to drug interactions. Use of corticosteroids and CYP3A4 inhibitors (e.g., ketoconazole and grapefruit juice) should be avoided, as it may cause increased systemic corticosteroid effects. Use with CYP3A4 inducers (e.g., barbiturates, phenytoin, carbamazepine, and rifampin) may require a dosage increase of the corticosteroid agent. Concurrent use with warfarin may cause a diminished anticoagulant effect; INR should be monitored. Adjustments in antidiabetic medication dosage may be required due to increased blood glucose levels. Increased activity of both cyclosporine and corticosteroids may occur with concurrent use; convulsions have been reported. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of GI side effects. Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia; patients should be observed closely, especially if on potassium-depleting medications.

Kaposi's sarcoma has been reported in patients treated with corticosteroids, primarily for chronic conditions. Clinical improvement may result if steroid therapy is stopped.

Based on observational studies, deflazacort may lead to an increased risk of thromboembolism and should be used with caution in patients who have or are predisposed to thrombotic disorders.

Serious skin rashes, such as toxic epidermal necrolysis, have been reported with use of deflazacort with symptoms reported within 8 weeks of starting treatment. Deflazacort should be discontinued at first sign of a rash, unless it is determined that it is not drug-related.

Patients with suspected or identified pheochromocytoma, are at increase risk of pheochromocytoma crisis, which can be fatal; risk of pheochromocytoma crisis should be considered prior to administering corticosteroids.

PLACE IN THERAPY[34,35,36,37,38,39]

Orally-administered glucocorticoids are very useful in reducing the signs and symptoms of various inflammatory and autoimmune conditions and for corticosteroid replacement therapy, as with Addison's disease. Betamethasone, dexamethasone, methylprednisolone, prednisolone, and prednisone are principally used as anti-inflammatory or immunosuppressant agents. Prednisone (Prednisone Intensol, Rayos) is generally considered the oral glucocorticoid of choice for anti-

inflammatory or immunosuppressant effects. Dexamethasone is also used as an anti-emetic for patients receiving antineoplastic therapy. Budesonide (Entocort EC) is only indicated for the treatment and maintenance of remission of mild to moderate active Crohn's Disease involving the ileum and/or the ascending colon; duration of maintenance therapy is up to 3 months.

Oral glucocorticoids are also indicated for use in the treatment of endocrine conditions, such as congenital adrenal hyperplasia, hypercalcemia of malignancy, nonsuppurative thyroiditis, and primary or secondary adrenocortical insufficiency. Cortisone and hydrocortisone are considered agents of choice for replacement therapy in patients with adrenocortical insufficiency due to their short biologic activity and their pharmacology, possessing both glucocorticoid and mineralocorticoid properties. Cortisone and hydrocortisone are not considered first-line for patients requiring anti-inflammatory or immunosuppressive effects.

Dosages of orally-administered corticosteroids should be individualized according to disease severity and patient response. The lowest effective dosage with the shortest duration possible should be prescribed to minimize adverse effects. Long-term therapy is generally not recommended. Dosages should be gradually tapered when discontinuing therapy, particularly if the patient has been on therapy for more than 6 weeks.

While select corticosteroids have been used historically to treat Duchenne muscular dystrophy (DMD), deflazacort (Emflaza) is the first steroid FDA-approved for this use. The 2016 guidelines by the American Academy of Neurology (AAN) for the corticosteroid treatment of DMD recommend offering prednisone (0.75 mg/kg/day) or deflazacort (0.9 mg/kg/day) to improve strength, pulmonary function, and motor function, and to reduce the need for scoliosis surgery, and delay cardiomyopathy.[40] Furthermore, deflazacort may by be offered to delay loss of ambulation and increase survival at 5 to 15 years of follow up. Corticosteroids may be used in combination with another agent for DMD, eteplirsen (Exondys 51™) as well. Notably, prednisone is not FDA-approved for DMD, but it has traditionally been used for this purpose and has evidence to support its use.

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